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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No. : 09/925,139 Confirmation No.: 3066

Applicant : Crooke et al.

Filed: : August 8, 2001

TC/A.U. : 1635

Examiner : J. Schultz

Customer No. : 36441

Title : ANTISENSE MODULATION OF CHOLESTERYL ESTER TRANSFER PROTEIN EXPRESSION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR §1.132

I, Dr. Susan Freier, a citizen of the United States, residing at 2946 Renault Street, San Diego, CA 92122, DO state the following:

1. I hold a B.A. in Mathematics (1972) from Carleton College, Northfield, Minnesota and a Ph.D. in Chemistry (1976) from the University of California, Berkeley, California.

2. I have been employed by Isis Pharmaceuticals, Inc. (hereinafter "Isis"), for about fourteen years. Isis, the assignee of the above-identified patent application,

specializes in oligonucleotide technology and uses the latest in bioinformatics programs to identify sites on selected genes for oligonucleotide screening.

I am presently the Executive Director of antisense lead identification at Isis and am responsible for a number of projects. I lead a project utilizing antisense oligonucleotides for functional genomics of novel targets, including the use of computational genomics to characterize target RNAs and their variants, rapid throughput screening to identify active antisense oligonucleotides for novel targets, and Q-RT-PCR and microarrays for expression analysis. I also lead a project for determining microRNA function in mammals, including the use of computational identification of miRNAs and miRNA targets and the use of functional genomics to characterize miRNA biology and identify therapeutic applications of modulation of miRNA activity. In addition, I lead a group charged with the identification and characterization of novel mechanisms for antisense oligonucleotides, including the use of computational genomics to identify mRNA variants, alteration of RNA processing, evaluation of siRNA and miRNA mechanisms. Another project I am responsible for involves biophysical and biochemical evaluation of novel antisense oligonucleotides, including the evaluation of thermodynamics and kinetics of hybridization to oligonucleotide and large structured targets, evaluation of the biochemical properties of novel oligonucleotides, characterization of antisense activity in cell assays, and protein-oligonucleotide binding.

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3. During the course of my employment at ISIS, I performed and supervised experimentation employing oligomeric compounds and inhibition of mRNA expression. My work has involved designing assays to screen oligomeric compounds against specific genes as well as interpreting the results from such assays. I have authored or co-authored numerous scientific journal articles regarding the same. I am an expert in the art of antisense technology and oligonucleotide screening. A copy of my *curriculum vitae* is attached as Exhibit 1.

4. I have reviewed the Office Action dated March 16, 2004.

5. This Declaration is filed to submit comments on statements in the Office Action regarding the motivation for combining the cited references and the alleged reasonable expectation of success by one of skill in the art for inhibiting the expression of any particular gene or mRNA with oligomeric compounds based only upon a given gene sequence.

6. It is **currently not** possible to predict **before** the appropriate experiment is performed on any particular target, which experiments will generate oligomeric compounds that will have a significant level of inhibition of target expression.

7. One skilled in screening of oligomeric compounds cannot, *a priori*, reasonably expect a significant level of inhibition of a gene or mRNA simply because methods of screening oligomeric compounds are available and/or routine. The statements in the Office Action regarding reasonable expectation of success are neither accurate nor capable of being supported.

8. Each gene is unique. For instance, if one skilled in the art achieved at least 50% inhibition in the expression of a first gene with oligonucleotides that are specific to the first gene, one skilled in the art ***would not*** reasonably expect success in achieving at least 50% inhibition in the expression of a ***different*** gene with a different set of oligomeric compounds that are targeted to the different gene or mRNA. The level of inhibition of expression that is observed for one target has no bearing on the level of inhibition of expression expected for a different target.

9. Taylor et al., ***1999*** Drug Disc. Today, 4(12):562 (hereinafter "Taylor") is a review article that makes unsupported assertions about the ease of identifying target sites on ***any*** gene for oligonucleotides that, upon binding to the target, can inhibit gene expression. The determination of target sites on a gene that permits one to identify suitable, highly inhibitory oligonucleotides for that gene is not a process that can be predicted to be easy or simple, based merely upon the identification of the gene

sequence of the target gene or even a suggestion that inhibition of a particular gene may be desirable.

10. Taylor also purports that only 3-6 oligonucleotides need to be screened in order to find an oligonucleotide that inhibits expression with 66-95% efficiency. Taylor, however, has numerous deficiencies that seriously impact its ability to teach one skilled in the art how to screen for such active oligonucleotides. For example, Taylor fails to identify the chemical modifications that make the oligonucleotides reported therein chimeric. In addition, Taylor fails to identify any bioinformatics program reported therein (particularly the one that apparently can screen as few as 6-9 oligonucleotides to find one that inhibits gene expression with 66-95% efficiency) by name. Indeed, I am not aware of any such computer program. Further, Taylor fails to identify the manufacturer of such a bioinformatics program reported therein. Taylor, rather than actually teaching sufficient details that would actually allow one skilled in the art to carry out screening methods with such fantastic results, simply refers to "unpublished data." Taylor also fails to teach how such results may be attained manually. Thus, Taylor acts only as general guide for screening oligomers and does not provide any details sufficient for one skilled in the art to carry out any particular methodology. Indeed, I am unaware of any algorithm or methodology presently available that would enable one either to predict *a priori* with such confidence whether a

particular level of inhibition of a gene or mRNA will occur.

11. As one of skill in the art and as an author of over 75 scientific references, the mere fact that Taylor published in a peer-reviewed journal *does not* mean that Taylor teaches how to practice that which it purports to teach.

12. Neither Baracchini et al., US Patent No. 5,801,154 (hereinafter "Baracchini") or Bennett et al., US Patent No. 5,955,443 (hereinafter "Bennett"), taken individually or together, compensate for the many deficiencies discussed above in relation to Taylor. Baracchini and/or Bennett fail to teach how to select target regions for the 3-6 oligonucleotides to be screened to be able to find an oligonucleotide that inhibits expression with 66-95% efficiency. Baracchini and/or Bennett also do not provide the identity of the computer program referred to in Taylor. Baracchini and/or Bennett further do not teach or suggest how such results may be attained manually. I could not practice the methods of selecting target regions described in Taylor, even in view of Baracchini and/or Bennett.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge

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that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Jun 16, 2004 By: Susan Freier

Susan Freier, Ph.D.

Attachments:

Curriculum vitae of Dr. Susan Freier